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Lymphatic Mapping and Sentinel Lymphadenectomy for Breast Cancer

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Objective

The authors report the feasibility and accuracy of intraoperative lymphatic mapping with sentinel lymphadenectomy in patients with breast cancer.

Summary Background Data

Axillary lymph node dissection (ALND) for breast cancer generally is accepted for its staging and prognostic value, but the extent of dissection remains controversial. Blind lymph node sampling or level I dissection may miss some nodal metastases, but ALND may result in lymphedema. In melanoma, intraoperative lymph node mapping with sentinel lymphadenectomy is an effective and minimally invasive alternative to ALND for identifying nodes containing metastases.

Methods

One hundred seventy-four mapping procedures were performed using a vital dye injected at the primary breast cancer site. Axillary lymphatics were identified and followed to the first ("sentinel") node, which was selectively excised before ALND.

Results

Sentinel nodes were identified in 114 of 174 (65.5%) procedures and accurately predicted axillary nodal status in 109 of 114 (95.6%) cases. There was a definite learning curve, and all false-negative sentinel nodes occurred in the first part of the study; sentinel nodes identified in the last 87 procedures were 100% predictive. In 16 of 42 (38.0%) clinically negative/pathologically positive axillae, the sentinel node was the only tumor-involved lymph node identified. The anatomic location of the sentinel node was examined in the 54 most recent procedures; ten cases had only level II nodal metastases that could have been missed by sampling or low (level I) axillary dissection.

Conclusions

This experience indicates that intraoperative lymphatic mapping can accurately identify the sentinel node—i.e., the axillary lymph node most likely to contain breast cancer metastases—in some patients. The technique could enhance staging accuracy and, with further refinements and experience, might alter the role of ALND.

The presence or absence of axillary lymph node metastases remains the most important prognostic factor in patients with potentially curable carcinoma of the breast, and the development of effective adjuvant systemic therapies has made recognition of these metastases critical for patient management. Historically, nodal involvement was determined by radical axillary lymph node dissection, usually as part of a radical mastectomy. Recent data suggest that less radical axillary procedures may result in adequate axillary staging and regional control, but the extent of such limited operations is a point of controversy. Underlying this controversy are questions concerning the accuracy of limited surgical staging and the role of axillary lymphadenectomy (ALND).

Noninvasive staging of the axilla is inadequate. Physical examination cannot accurately predict axillary lymph node metastasis.[1] Furthermore, lymphangiography has not reliably demonstrated nodal disease.[2] A recent study used positron emission tomography (PET) with intravenous 18-fluoro-2-deoxyglucose (FDG) to demonstrate primary breast carcinoma and regional metastases;[3] however, results are preliminary, and the limits of detection and size of detectable lesions or metastases are unknown.

Definitive diagnosis of axillary metastasis in patients with breast cancer requires excision and histologic examination of axillary lymph nodes. How many nodes should be removed to ensure accurate staging? Although ALND remains the "gold standard" for sensitivity and accuracy of detection, it carries a higher morbidity than sampling techniques. Morton and others[4] have demonstrated the accuracy of intraoperative lymphatic mapping and selective sentinel lymphadenectomy to identify lymph node metastasis in patients with primary cutaneous malignant melanoma, reporting a false-negative rate of less than 1% in more than 500 cases. This high degree of accuracy has been substantiated at other institutions where patients with melanoma are treated.[5] We developed and used a modification of lymphatic mapping and sentinel lymphadenectomy to detect axillary lymph node metastasis in patients with breast carcinoma.

PATIENTS AND METHODS

Patients with potentially curable breast carcinoma who were undergoing ALND as part of their standard treatment were evaluated. Patients with prior axillary operations (dissection/excisional biopsy) were excluded. Each patient underwent intraoperative lymphatic mapping and sentinel lymphadenectomy during modified radical mastectomy or segmental mastectomy with ALND. All operations were performed by the same surgeon, who had no prior experience with lymphatic mapping and sentinel lymphadenectomy. Informed consent was obtained in all cases.

The technique of lymphatic mapping and sentinel lymphadenectomy for melanoma, described in detail elsewhere,[6] was modified for patients with breast cancer. After induction of general anesthesia, isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Inc., Richmond, VA) was injected with a 25-gauge needle into the breast mass and surrounding breast parenchyma. The first 20 patients received 0.5 to 10 mL of dye; in subsequent cases, the dose was standardized at 3 to 5 mL. If the primary tumor had been excised previously, the dye was injected into the wall of the biopsy cavity and surrounding breast parenchyma through several points along the incision.

During the first 20 cases, the interval between dye injection and axillary incision was varied from 1 to 20 minutes to determine the time required for dye to reach the axillary drainage basin. A standard interval of approximately 5 minutes was used in the remaining cases. A transverse incision was made just below the hair-bearing region of the axilla. Blunt dissection was performed until a lymphatic tract or blue-stained node was identified. The dye-filled tract was dissected to the first blue lymph node. If possible, the tract was followed proximally to the tail of the breast to ensure that the identified lymph node was the most proximal lymph node and thus, the sentinel node. This lymph node was excised with a rim of sur-

Table 1. PATIENT DEMOGRAPHIC INFORMATION

Total no. of cases	174
Total no. of patients	172
Mean age	56 yrs
Age range	29–84 yrs
Premenopausal	74 (43.0%)
Postmenopausal	98 (57.0%)
Mode of tumor detection	
Physical examination	109 (63.3%)
Mammography	65 (37.7%)
Operative procedure	
Breast-conserving surgery*	142 (81.7%)
Modified radical mastectomy	32 (18.3%)

* Segmental mastectomy and axillary lymphadenectomy.

Table 2. SIZE OF PRIMARY TUMOR AND HISTOLOGIC STATUS OF AXILLARY NODES

Size of tumor	
Tis	15 (8.6%)
T1	104 (59.8%)
T2	37 (21.3%)
T3	18 (10.3%)
Histologic status of axillary nodes	
Tumor-positive	62 (35.6%)
Tumor-negative	112 (64.4%)

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rounding tissue and submitted as a separate specimen for histologic examination using hematoxylin and eosin (H & E) staining.[6]

For patients undergoing segmental mastectomy, ALND was completed, and the primary breast tumor was excised through a separate incision. For patients undergoing modified radical mastectomy, the mastectomy with en bloc axillary dissection was completed. All ALND procedures included level I, level II, and at least some level III nodes; the pectoralis minor muscle was left intact. If gross lymph node metastases were evident in sentinel or nonsentinel nodes, complete level III dissection was performed. All nodes in the ALND specimen were processed for histologic examination using H & E. Lymph node clearance techniques to identify additional nodes were not performed.

Figure 1. Two side-by-side, blue-staining sentinel lymph nodes and lymphatic tracts *in situ*.

Histologic Examination

All axillary specimens were examined by pathologists at Saint John's Hospital and Health Center. Fixed sections of false-negative sentinel nodes were examined retrospectively with immunohistochemical techniques, using antibodies to cytokeratin.

Statistical Analysis

Data were analyzed by the members of the Biostatistical Unit at the John Wayne Cancer Institute and the University of California at Los Angeles. A likelihood ratio chi square test was used to compare the difference between two proportions. The statistical package of SAS procedures, FREQ, was used in the analyses.

RESULTS

Between October 1, 1991 and February 1, 1994, 172 women underwent intraoperative lymphatic mapping and sentinel lymphadenectomy immediately before modified radical mastectomy or breast-conserving surgical treatment of primary breast carcinoma. Their mean age was 56 years (range 29–84 years). Menopausal status, mode of tumor detection, and operative procedures are listed in Table 1. Because two patients presented with synchronous bilateral breast primaries, there were 174 surgical procedures: 142 (81.7%) segmental mastectomies with ALND and 32 (18.3%) modified radical mastectomies.

Tumor size and histologic axillary nodal status are listed in Table 2. Of the 23 patients whose preoperative clinical assessment indicated axillary involvement, 6 (26.0%) had histologically negative nodes; of 151 patients with clinically negative axillary nodes, 45 (29.8%) had histologic evidence of axillary metastasis. The sensitivity of clinical examination was 27.4%, with a specificity of 94.9%.

The blue-staining sentinel lymph node was identified in 114 of 174 (65.5%) procedures. More than one lymph node often was found in the sentinel lymphadenectomy specimen, for a total of 207 sentinel nodes. Figure 1 shows blue-staining sentinel lymph nodes and lymphatic tracts *in situ*. There was a clear learning curve; the surgeon's rate of sentinel node detection increased with experience (Fig. 2). Sentinel nodes were detected in 51 (58.6%) of the first 87 mapping procedures and in 63 (72.4%) of the last 87 procedures. In the last 50 cases, the rate of detection was 78.0%.

The accuracy of lymphatic mapping was examined by comparing the histopathology of sentinel node and nonsentinel node (ALND) specimens. The sentinel node accurately identified axillary nodal status in 109 of 114 cases (95.6%; Table 3). In 5 of 114 cases (4.3%), the sentinel node was falsely negative, i.e., no tumor was identified in the sentinel node, but at least one nonsentinel node harbored metastasis. All false-negative sentinel nodes occurred in the first 87 cases, most in the first 50 cases (Fig. 3). The overall sensitivity of the sentinel node technique was 88.0%, with a specificity of 100%. The overall positive and negative predictive values were 100% and 93.5%, respectively. In the last half of the study, the positive and negative predictive values were 100% and 100%, respectively.

The five false-negative sentinel node specimens were retrospectively re-examined and then studied with an immunohistochemical technique using antibodies to cytokeratin. Three (60.0%) specimens contained <2 mm foci of lymphoid tissue in several centimeters of fat; these specimens had been misinterpreted as lymph nodes. One (20.0%) sentinel lymph node stained positive for metastatic breast cancer by immunohistochemistry; the fifth sentinel node (20.0%) remained negative.

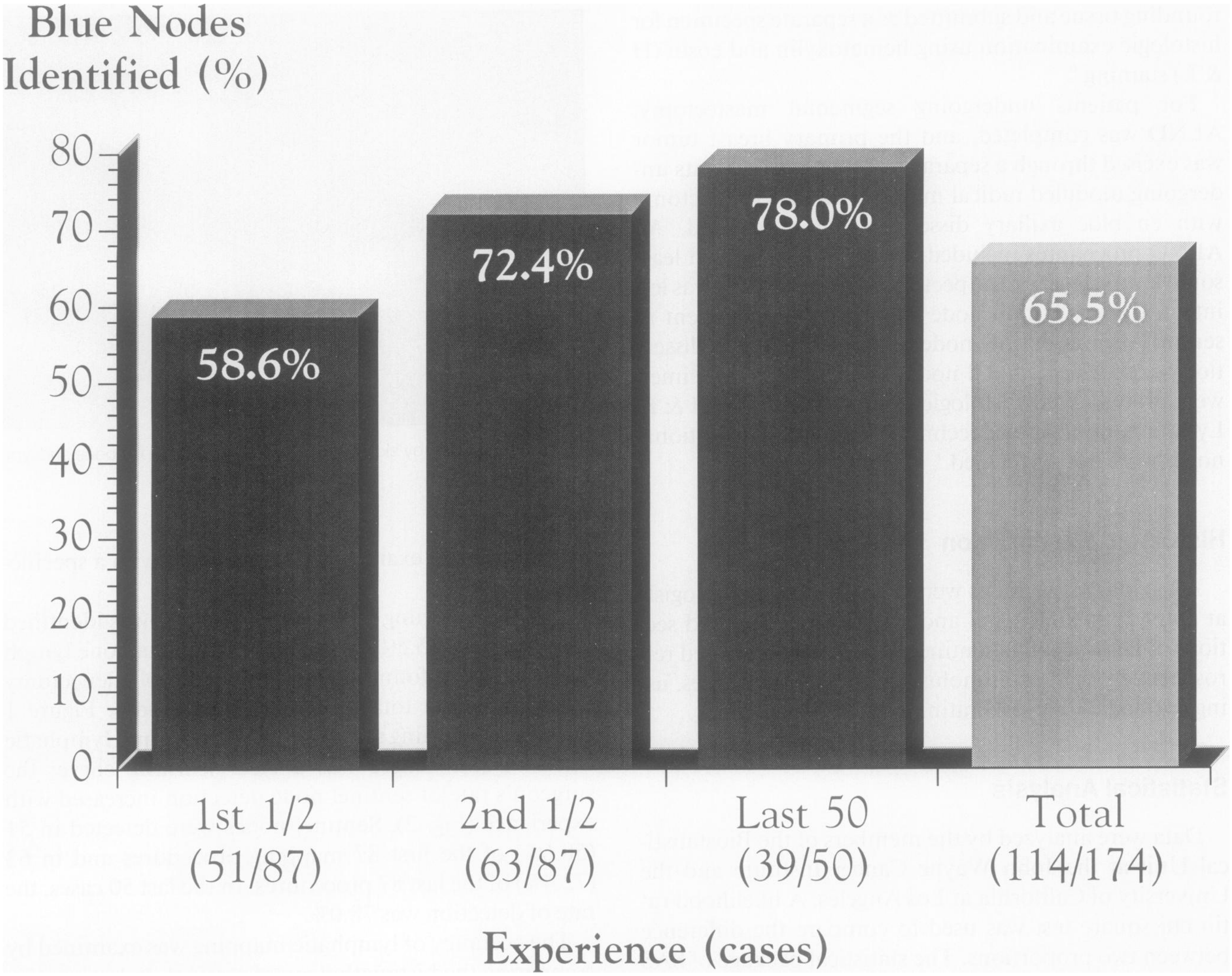

Figure 2. The incidence of blue node detection according to the surgeon's experience with lymphatic mapping and sentinel lymphadenectomy.

To determine whether the uptake of dye by lymph nodes containing metastases was random, we analyzed the 14 cases in which only one tumor-positive lymph node and at least one sentinel node were identified (Table 4). Of 285 total lymph nodes examined in these 14 cases, 18 were sentinel; tumors were found in 13 of 18 (72.2%) sentinel nodes and only 1 of 267 (0.37%) nonsentinel nodes ($p < 0.00001$; likelihood ratio chi square analysis). Thus, it was highly unlikely that uptake of dye by an involved node was a result of chance alone.

Table 3. DISTRIBUTION OF METASTASES IN SENTINEL AND NONSENTINEL LYMPH NODES

Total no. of mapping procedures	174
Total no. of positive axillary basins	62 (35.6%)
No. of successful mapping procedures*	114 (65.5%)
No. of positive sentinel node specimens	37 (32.4%)
No. of falsely negative sentinel node specimens	5 (4.3%)
Sentinel and nonsentinel nodal histology in agreement	109 (95.6%)

* Sentinel node(s) identified.

We also compared the sensitivity of lymphatic mapping and sentinel lymphadenectomy with that of random (blind) biopsy. We calculated the probability of detecting nodal metastases using each of these techniques in 34 clinically negative/histologically positive axillae in which a sentinel node was identified. The 34 dissections yielded a total of 751 lymph nodes; 132 were tumor-positive. In these axillae, there were 63 sentinel nodes; 39 were tumor-positive. Therefore, in patients with subclinical axillary metastases, the probability of excising a positive node using random sampling was 132/751 (17.5%) *versus* 39/63 (61.9%) using lymphatic mapping ($p <$

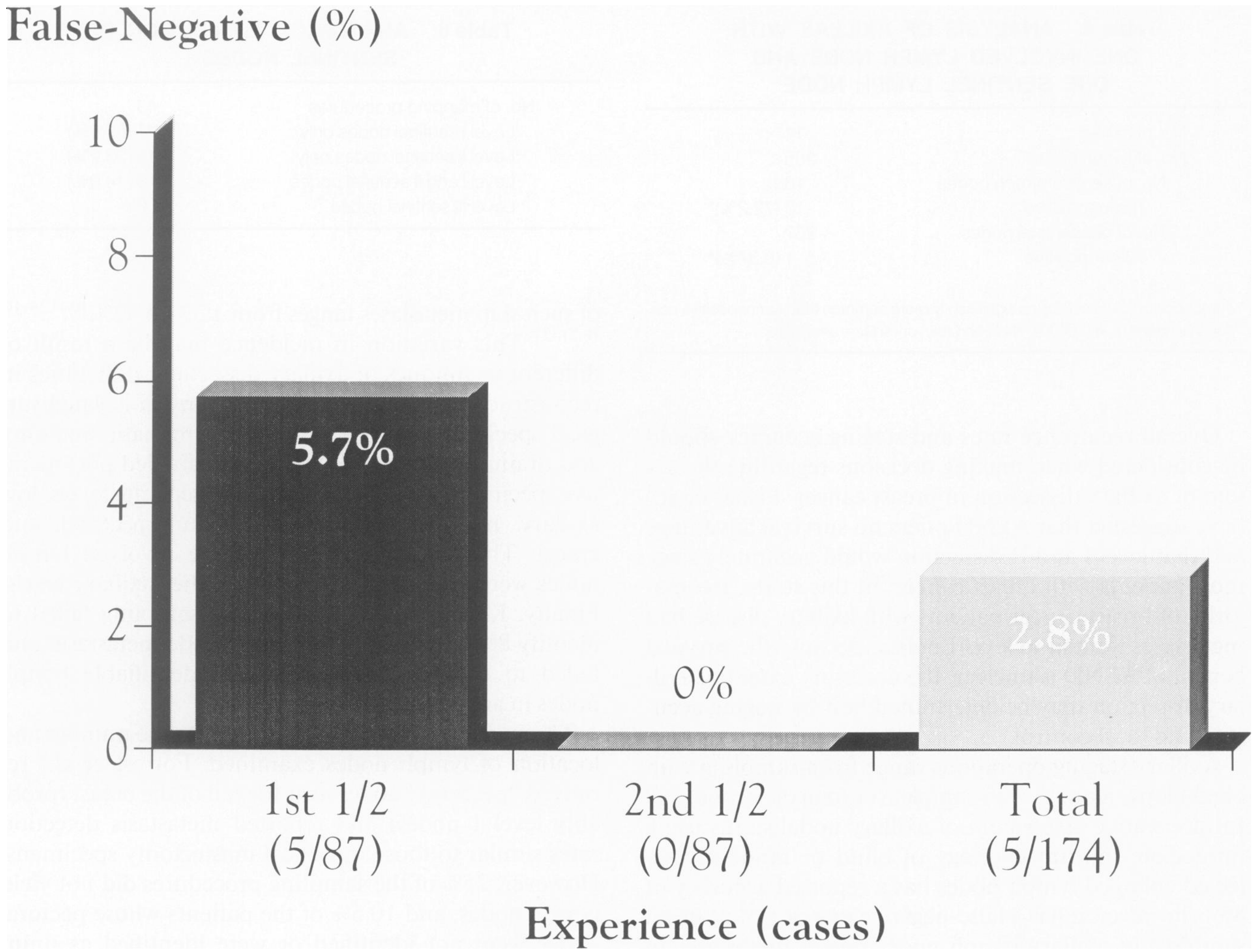

Figure 3. The incidence of false-negative sentinel nodes according to the surgeon's experience with lymphatic mapping and sentinel lymphadenectomy.

0.0001; likelihood ratio chi square analysis) (Table 5). In 16 of 42 total cases (38.0%) with clinically negative/pathologically positive axillae, sentinel nodes were the only positive lymph nodes identified.

At the time of operation, we recorded the anatomic level of the sentinel node in the 54 most recent cases (Table 6). Of 43 cases in which the sentinel node was identified, 27 (62.7%) had sentinel nodes only in level I, whereas 10 (23.7%) exhibited "skip" drainage of isosulfan blue dye to sentinel nodes in level II but not level I. The remaining six cases had blue-staining sentinel nodes in levels I and II.

DISCUSSION

Determination of axillary nodal status is essential for the staging of breast cancer. However, the extent of axillary dissection required for accurate staging is controversial. Total dissection of the axilla has the highest morbidity,[7] but offers the greatest staging accuracy. The accuracy of limited dissections or sampling procedures is unclear, partially because these procedures often are ill defined and partially because of the methods used to evaluate their accuracy. Differences in staging techniques are best described by Kinne.[8] Sampling is the removal of an axillary node or nodes from the lower axilla without defining precise anatomic boundaries. Low axillary dissection is an en bloc excision of level I lymph nodes, defined anatomically as lymph nodes medial to the latissimus dorsi muscle and extending to the lateral border of the pectoralis minor muscle and the axillary vein cephalad. Level I and II dissection is an en bloc excision of the low and middle portions of the axilla; dissection extends from the latissimus dorsi to the medial edge of the pectoralis minor and to the axillary vein. Total axillary dissection (levels I, II, and III) removes the entire contents of the axilla from the latissimus dorsi laterally to the subclavius muscle (Halsted's ligament) medially.

Table 4. ANALYSIS OF AXILLAE WITH ONE INVOLVED LYMPH NODE AND ONE SENTINEL LYMPH NODE

No. of axillae	14
No. of lymph nodes	285
No. of sentinel lymph nodes	18
Tumor-positive	13 (72.2%)*
No. of nonsentinel nodes	267
Tumor-positive	1 (0.37%)*

* Tumor-positive sentinel nodes significantly more common than tumor-positive nonsentinel nodes ($p < 0.00001$, likelihood ratio chi square analysis).

Table 6. ANATOMIC DISTRIBUTION OF SENTINEL NODES

No. of mapping procedures	43
Level I sentinel nodes only	27 (62.8%)
Level II sentinel nodes only	10 (23.2%)
Level I and II sentinel nodes	6 (14.0%)
Level III sentinel nodes	0

Overall recurrence rates and staging accuracy should be considered when making decisions regarding the extent of axillary dissection in breast cancer. Fisher et al.[1] have suggested that ALND offers no survival advantage and that level I and II dissection would accurately stage most patients with breast cancer; in this study, the majority of breast cancer patients with axillary disease had metastases limited to level I nodes. Because the survival benefit of ALND is unclear, the necessary extent of axillary dissection may be determined best by staging accuracy and local control.

Axillary staging operations range from sampling with blind biopsy alone[1,9-13] to complete or total dissection.[14-20] Intraoperative assessment of axillary nodal status using immediate imprint cytology of blind or randomly selected enlarged lymph nodes has a reported accuracy of 85%; however, it has a false-negative rate of 14%.[13] Blind sampling of axillary lymph nodes misses metastases in 15% to 42% of cases.[13-18] In a study of patients undergoing radical mastectomy, Davies et al.[15] removed fibroadipose tissue from approximately the level of the third rib, immediately before ALND. Forty-two per cent of these tissue specimens were tumor-negative, whereas higher-level lymph nodes in the corresponding ALND specimen were tumor-positive. The reported incidence of such skip metastases ranges from 1.3% to 42%.[10,11,14-16,18,21-23] This variation in incidence may be a result of different techniques of axillary dissection, difficulties in reconstructing normal axillary anatomy in isolated surgical specimens, and variations in lymphatic anatomy and drainage patterns. Sarce et al.[18] divided postoperative specimens into the following five separate levels: low axillary, midaxillary, high axillary, interpectoral, and apical. They found that 15% of the involved lymph nodes were identified only in the higher axillary levels. Finally, Kissen et al.[17] showed that sampling failed to identify 8% of patients with lymph node metastases and failed to obtain a specimen with identifiable lymph nodes in another 10% of patients.

Table 5. ANALYSIS OF CLINICALLY NEGATIVE/HISTOLOGICALLY POSITIVE AXILLAE CONTAINING IDENTIFIABLE SENTINEL NODES

No. of clinically negative/histologically positive axillae	34
No. of nodes excised	751
No. of sentinel nodes	63 (8.3%)
Tumor-positive	39 (61.9%)*
No. of nonsentinel nodes	688 (91.7%)
Tumor-positive	93 (13.5%)

* Sentinel node significantly more likely to contain tumor than nodes selected by random biopsy ($p < 0.0001$, likelihood ratio chi square analysis).

The accuracy of sampling is related to the number and location of lymph nodes examined. Forrest et al.[9] removed "pectoral" nodes near the tail of the breast (probably level I nodes) and reported metastasis detection rates similar to those in radical mastectomy specimens. However, 25% of the sampling procedures did not yield lymph nodes, and 10.5% of the patients whose pectoral nodes were not identified or were identified as uninvolved with tumors developed regionally recurrent disease. Forrest et al.[10] demonstrated an 8% false-negative rate in specimens with three to four lymph nodes, and Steele et al.[12] suggested that removal of at least four nodes from the lower axillary fat pad near the tail of the breast was as accurate as ALND.

Kjaergaard et al.[24] showed that axillary recurrence in breast cancer patients with low-risk primary lesions decreases as the number of excised lymph nodes increases. Their rate of axillary recurrence resulting from missed or untreated disease was 12% when no nodes were removed, 7% when two lymph nodes were removed, and only 2% when more than three lymph nodes were removed. In a similar study, Graversen et al.[25] reported a 3% rate of axillary recurrence after removal of five to ten axillary lymph nodes. Mathiesen et al.[26] suggested ten as the minimum number of excised nodes for an adequate sampling procedure.

Axillary recurrence is associated with the number of metastatic nodes,[27] especially when four or more nodes are involved or fewer than ten nodes have been sampled.[28] Complete axillary dissection markedly decreases the incidence of axillary recurrence.[29,30] Benson et al.[31]

demonstrated a statistically significant decrease in axillary recurrence rate among patients receiving complete nodal dissection, described as levels I and II, when compared to a sampling procedure similar to the pectoral node procedure. This difference in regional recurrence was seen in patients with positive nodes and patients with negative nodes. Complete axillary dissection results in recurrence rates approaching zero at 50 months and provides accurate staging.[20]

The accuracy of sampling only can be equivalent to complete node dissection if sampling procedures included enough lymph nodes to detect skip metastases to any level of the axilla. The number of nodes also must be large enough to detect metastatic involvement by chance alone. The importance of accurate axillary staging to select candidates for adjuvant therapy has led most authorities to recommend level I and II axillary dissection for patients with breast cancer, despite the apparently low rate of skip metastases. This is summarized in a 1992 consensus statement from the National Cancer Institute.[32]

We have demonstrated a technique that appears to identify specific lymph nodes draining specific primary breast cancer sites. Excision of these sentinel nodes alone should have an extremely low morbidity and a high degree of staging accuracy. In our study, sentinel lymph nodes were significantly more likely to contain metastases than nonsentinel lymph nodes removed during ALND. In the second half of this study (87 patients), the sentinel node accurately predicted tumor involvement of the axilla in every patient.

Although most of the sentinel nodes were in anatomic level I of the axilla, 23.3% of our most recent dissections yielded a sentinel node in level II alone. Because the sentinel node was the only positive lymph node in 38% of tumor-positive axillary basins, a blind sampling procedure or a level I dissection could miss involved sentinel nodes in level II. Although Veronesi et al.[21,23] proposed an orderly progression of tumor cells from level I to level II and then to level III, our data suggest that metastatic spread to the axilla is determined by the specific lymphatic drainage of the primary tumor, which in turn depends on each patient's lymphatic anatomy.

The ability to identify a tumor-free sentinel lymph node could enable the surgeon to accurately stage node-negative breast cancer patients without subjecting them to the morbidity of a formal dissection. Total ALND could be reserved for those patients proven to have regional axillary nodal metastases. Because we believe that the accuracy of sentinel lymphadenectomy in breast cancer should be equivalent to its accuracy in malignant melanoma, we are investigating methods to increase the rate of identifying the sentinel node and detecting nodal metastases. The findings for lymphatic mapping and sentinel lymphadenectomy, if confirmed, could have significant implications. Axillary mapping with sentinel lymphadenectomy enhances the accuracy of surgical staging and also may improve histologic staging by enabling the pathologist to focus on fewer lymph nodes. Further, metastases in the axilla may occur in an orderly fashion by appearing first in the sentinel lymph node. Nodal metastases that appear to skip an axillary level may result from variations in regional lymphatic drainage rather than nonsequential progression of tumor cells. Lymphatic mapping and sentinel lymphadenectomy should diminish staging morbidity and could alter the surgical management of the axilla in women with breast cancer.

Addendum

Since this manuscript was submitted, the authors have experienced one false-negative sentinel node. Thus, the false-negative rate since the first 87 cases is 1 of 137 (0.73%), equivalent to the false-negative rate in melanoma.

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Discussion

DR. KIRBY I. BLAND (Providence, Rhode Island): First let me begin by congratulating the authors, Dr. Giuliano, Dr. Morton and associates, for bringing this important new technique to the attention of the Association,

As the authors have properly emphasized. axillary lymph node dissection is essential to address the proper therapy both in the adjuvant as well as the therapeutic setting for invasive breast carcinoma. The difficulty, however, with blind sampling of Level 1 and 2 axillary nodes is the fact that the surgeon would frequently miss pathologically positive nodal metastases.

Most clinics in North America and Europe currently recommend the sampling of a minimal ten nodes to accurately predict the extent of regional disease. Numerous studies have correlated the number of nodes to disease-free survival and overall survival; therapy schedules are often designed for the number of pathologically positive nodes. As an example, as you know, young women with ten or more nodes today very commonly are relegated to autologous bone marrow transplantation.

The authors should be acknowledged for their important contribution to intraoperative lymph node mapping with sentinel lymphadenectomy for intermediate thickness melanoma. And now we see if for breast carcinoma staging.

Although I was originally skeptical about the application of these techniques for melanoma, with increasing usage I have now become comfortable with the technique for preoperative lymphoscintigraphy to assist identification of sentinel nodes and the vital blue dye Azozurin (TM) to actually provide you with visual identification of the first echelon of these potential metastases.

This technique is efficacious, cost-effective, and provides a very high predictive value, as Dr. Giuliano just showed us, for metastasis. The authors now have confirmed similar value for breast staging. The breast, however, often has variable and multidirectional distribution of lymphatic flow; this is especially true of medial quadrant and central lesions.

This study concluded that overall, two thirds of the sentinel nodes were identified; however, in the latter phases you have shown us that all the lymphatics could be identified in sentinel sites. Importantly, the accurate pathological node status was determined in 96% of these cases. Armando, my first question to you would be, how might we increase the yield to identify all sentinel nodes? Is this simply a function of familiarity with the technique? Are there other issues that you perhaps should address?

Secondly, lymphoscintigraphy using subdermal injections with technetium sulfur colloid or albumin is an extremely advantageous technique for mapping of cutaneous melanoma lymphatic distribution. Will your future approaches, perhaps, for mapping be inclusive of this technique either prior to or synchronous with the injection of isosulfan blue?

Your study has suggested statistically significant value to predict positive nodal disease when only one sentinel node is identified. You identified tumor-positive nodes in 72% of these patients in the sentinel node sites. That's compared with only 1% or less if the nodes were nonsentinel in location. You found essentially the same thing, however, in the clinically negative node-positive axilla. Your numbers were 62%; but on the other hand you've had an increase of over 30-fold to 14% for finding node-positive disease in nonsentinel sites.

So I'd ask you again, would lymphoscintigraphy perhaps have enhanced the probability of selective biopsy of these vital dye stained nodes? This is an important consideration because